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In 1897[1] the writer showed that the "pulsus regulariter intermittens" of the frog is a result of slowed conduction between sinus and auricle[2] or between auricle and ventricle; this was later accepted by Wenckebach[3] and further proof given by Mackenzie[4] for man. The problem of the pulsus alternans, however, has not profited by the application of physiology to the diseased heart. It is true, that a long time ago Traube directed attention on those types of P.A. in which the period between the weak beat and the next stronger one is smaller than between the larger and the smaller contraction, where W.O.W. the greater contraction commences too early. But up to the present only Oehrwall[5], W. Straub[6] and Trendelenburg[7] have gone into the analysis of allied heart-curves of the frog on the lines which have led to the elucidation of the intermittent pulse.

The alternating contraction of the ventricle is not a simple pathological phenomenon but rather a general physiological function, that makes its appearance in many circumstances, and which tends to appear both in vertebrates and in invertebrates in certain conditions. We have, in fact, to deal with a capacity of the cardiac muscle which enables the ventricle to go on with rhythmical contractions even under abnormal conditions.

Digitalis[8], injected subcutaneously in the frog, brings about peculiar changes in the heart-beat, after a certain period of normal contractions. In the transition of the normal period into the period of slow contractions,

[1] *Geneesk. Bladen.* 4e Reeks, p. 77. 1897.
[2] *Amer. Journ. of Physiol.* I. p. 509. 1898.
[3] Wenckebach. *Nederl. Tydschr. v. Geneesk.* I. p. 666. 1899.
[4] Mackenzie. *Brit. Med. Journ.*, 24 Oct. 1906.
[5] Oehrwall. *Skand. Arch. f. Physiol.* VIII. 1898.
[6] Straub. *Arch. f. Pathol. u. Pharmakol.* XLV.
[7] Trendelenburg. *Arch. f. (Anat. u.) Physiol.* p. 284. 1903.
[8] The digitalis used was digitalis dyalisata.

curves are regularly recorded which, together with curves of the dying frog-heart formerly published[1], throw light on one of the varieties of P.A. Three varieties at least must, in my opinion, be distinguished; as to the other types, I think that the way may become clear to explain them also.

First form of P.A. with equal intervals.

The ventricle beats in regular rhythm alternately stronger and weaker, the beginning of the weak contraction is separated by the same length of time from the preceding and following contraction (Fig. 1).

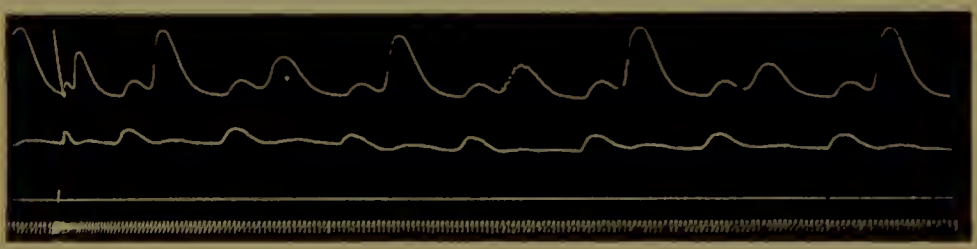

Fig. 1. Example of pulsus alternans of the frog[2] after injection of digitalis dyalisata, with equal intervals between the commencement of the small and large contractions. This tracing leaves no doubt that the larger contraction cannot be ascribed to a preceding longer rest.

This variety was described by Engelmann[3] and ascribed to momentarily diminished conductivity. F. B. Hofmann[4] has shown that this form of P.A. is often dependent on slight changes in the frequency of the heart-beat. Straub proved that this P.A., under the influence of antiarine, easily gives way to "Puls-Halbirung"; this I often saw under the influence of digitalis.

The absolutely equal intervals, with which in this tracing the small and the greater contractions follow upon each other, appear to me to disprove conclusively the theory advanced by Wenckebach, who was, no doubt, misled by the fact that in most tracings of human alternans the large beat usually comes too late. Wenckebach supposed that after a longer interval the ventricular musculature had had more time to recover its readiness to contract than after a small interval.

[1] *Nederl. Tydschr. v. Geneeskunde*, II. no. 12. 1902.
[2] All specimens are taken of *Rana temporaria*.
[3] Engelmann. *Arch. f. d. ges. Physiol.* LXII. p. 556. 1896.
[4] Hofmann. *Ibid.* LXXXVII. p. 165. 1900.

Second form of P.A. with retarded small contraction.

In a former publication[1] I described an example of P.A. observed in the dying frog-heart, where the interval between the greater and smaller V_s was longer than that between the smaller and larger contraction. There it appeared that the auricle continued to beat regularly. By comparing the intervals $A—V$, preceding the greater and smaller contractions, we concluded then that the contraction-wave in the $A—V$ bundle (or in the ventricle itself) might be slowed and that, in consequence, not only the V_s came too late, but also was weaker.

The supposition that this P.A. in certain cases might depend on changes of conductivity within the ventricle, was a proper subject for discussion, although, as remarked by Wenckebach, it could not be strictly proved. For one can never be certain of a change of conductivity within a heart cavity (*f.i.* within V) if the interval between the contractions of two cavities (*f.i.* $A—V$) remains equal. But this meritorious observer is mistaken if, from the few curves (10*a* and 10*b*) of Engelmann, he generalises to the contrary, i.e. to the exclusion of a similar relation in other cases. These curves cannot be looked upon as decisive on this point, because the auricles were not, as in my cases, beating regularly, and therefore entirely different factors must be present. He appears to disregard the fact that in lower animals it has been shown that under the influence of the vagus nerve the conductivity can be improved in one cavity, and at the same time can be inhibited in others. This was confirmed by Engelmann, when he observed how, in the three bridges, veins-sinus, sinus-auricle, auricle-ventricle, conductivity might be changed independently of each other. Only, then, very direct proof could force us to admit that under pathological circumstances this independence of conductivity is lost. So also Wenckebach's explanation of the early smaller contraction by the quicker course of the weaker pulse-wave in the vessels, appears to me to be open to discussion. Further, his conclusion that there is no essential difference between P.A. with too early and retarded small contraction wave does not appear to be warranted by any well-known fact, certainly not by Wenckebach's suppositions. Sufficient facts can be adduced now that in different ways the same result can be arrived at.

To my former curves of P.A. brought about by poor nutrition, I now can reproduce similar curves of P.A. brought about by injection of digitalis (Fig. 2).

[1] *Nederl. Tydschr. v. Geneesk.* II. 591. 1902.

In this case the interval $Si_s—V_s$ can be easily determined. This amounts to 20, 6 ; 22, 3 ; 20, 9. In every case this interval is lengthened where it precedes a smaller contraction ; i.e. the contraction-wave, which culminates in a smaller V_s, found more resistance on its road from the sinus to the ventricle and there was an undoubted slowing of the conduction.

Fig. 2. Tracing of P.A., where the larger contraction commences somewhat too late, and where alternately every weaker contraction of the ventricle is preceded by a weaker and dissociated contraction of the sinus. Also the auricular contraction appears alternately smaller if a line is drawn through the tops of the different A_s.

Looking carefully at the curve, one finds that the sinus contraction preceding a weak V_s shows a flattened top. By measuring the intervals of Si_s it becomes equally clear that the sinus does not contract regularly and that it is the sinus contraction, coming too early, that is followed by a smaller V_s. Also the A_s preceding the weak V_s appears to be diminished in size.

Although it is not the place here to go into detail about the fact that there exists a relation between the force of the sinus and auricular contraction and the force of the ultimate V_s, I will only remark that in many similar experiments this relation was found. The question arises, indeed, if different parts of the three principal heart-cavities do maintain a special relationship in such a way that a completer sinus and auricular contraction tends to give rise to a completer ventricular contraction. If so, the next problem appears to be whether this relation is kept up by special muscular arrangements or whether nervous and ganglionic influence may play a *rôle* in it.

Third form of P.A. with retarded smaller contraction.

Fig. 3 is an example where we find reappearance of normal pulsation. Simple inspection of the pulsating heart gave me the impression that there was an antiperistaltic contraction; that the contraction-wave, reaching the ventricle from the auricle, returned

again to the auricle. Brandenburg[1], Pan[2], Hering[3], Volhard[4] and Schmoll[5] have observed antiperistaltic contraction. I showed long ago[6] that antiperistaltic contractions are a very constant phenomenon in the sinus of the turtle-heart.

Fig. 3. Temporary P.A. after injection of digitalis dyalisata. The first V_s is normal; the second is somewhat smaller; then follows a lengthened contraction; then an antiperistaltic A_s and V_s. Then, again, the normal pulsation sets in.

In the case of Fig. 3 we have to deal with two possibilities; first we may have to do with a real extra-contraction of the auricle and ventricle, which results only in a very small elevation of the lever, because of its appearing in the beginning of the diastole, the ventricle being in the refractory period; or, secondly, we may have to do with an antiperistaltic contraction-wave which, on account of insufficient restoration of conduction in the $A—V$ bundle and the ventricular musculature, can only give rise to a weak V_s.

The first supposition could not be discarded if one could admit that spontaneously in similar conditions in the frog such an extra A_s, followed by a very weak V_s, could occur; i.e. an extra-contraction followed by an incomplete compensatory pause. This conception is however hardly acceptable if we take note of the regular mode in which this P.A., so to say, is prepared by the two abnormal contractions, which precede the very small V_s. Since these changes in the two ventricular contractions occur regularly (at least in so far as in my curves I come across similar cases), I think that the other interpretation gains considerably in probability. My supposition is therefore as follows: Under the influence of the drug the conducting power within the ventricle is

[1] K. Brandenburg. *Arch. f. Anat. u. Physiol.* 1904. Supp. p. 216.

[2] O. Pan. *Deutsche Zeitschr. f. klin. Med.* LXXVIII. p. 128. 1903.

[3] Hering. *Pflüger's Arch.* LXXXII. p. 1.

[4] Volhard. *Zeitschr. f. klin. Med.* LIII. p. 574. 1904.

[5] Schmoll. *Arch. f. klin. Med.* p. 507. 1907.

[6] *Ned. Tydschr. v. Geneesk.* II. p. 568. 1898; and *Amer. Journ of Physiol.* I. p. 504. 1898.

sensibly reduced. In the first, slightly weakened, V_s only a part of the ventricular musculature could contract as a result of this disturbance of conduction. In the next V_s, however, the contraction wave spreads more slowly than normal (hence the stretched form of V_s) over the entire ventricular musculature. Whereas the conducting power through the ventricular musculature can take place after the modern doctrine of Gaskell and Engelmann in all directions, the contraction wave winds its way through this lengthened V_s to arrive antiperistaltically again at the auricle. After this, only a part of the ventricular musculature has regained its conducting power sufficiently, and a weakened V_s will join the antiperistaltic A_s. It is clear that on account of the antiperistaltic contraction from A to V, to A again; from A returning to another limited part of V; then again A, etc., will give rise to a pulsus alternans, in this case temporarily, whereby the interval between the commencement of the large contraction and that of the smaller one is greater than that between the commencement of the small and that of the larger contraction. In the digitalis experiments one can recognise these cases, where, after a maximal toxic dose, the frequency first became considerably slower, but finally quicker again. Whereas in the vena cava curve the pulsations of the sinus were previously easily visible, one does not find any indication of sinus contraction after the premortal pulse acceleration has set in.

Here, therefore, we find a form of cardiac activity, which shows the same peculiarities as the P.A. formerly described by the writer in the poorly nourished frog-heart (*loc. cit.* 1902) of which, however, the mode of origin was quite a different one.

The only objection which can be adduced against this interpretation is a theoretical one. It has been looked upon as a dogma that the unimpaired ventricular musculature under no circumstances shows the phenomena of dissociation. This dissociation between the different heart-cavities and in every one separately was explicitly described by the writer in several publications[1], especially regarding the sinus; its significance for our understanding of nerve influence on the heart was more than once urged. Although in these experiments and those of Engelmann the occurrence of similar dissociations of the unimpaired ventricle had also to be acknowledged, the direct proof of its existence, as far as I know, has never been given. When, under the influence of

[1] *Geneesk. Bladen.* p. 75. 1897. *Proc. of the Amer. Acad. of Arts and Sci.* XXXIII. p. 188. 1898. *Amer. Journ. of Physiol.* p. 503, etc. 1898. *Ned. Tydschr. v. Geneesk.* II. p. 572. 1898 and II. p. 583, etc. 1902.

digitalis, the tendency of the cardiac muscle to dissociation is accentuated, we should expect, if we combine this influence with the equally dissociating vagus influence, to find evidence of dissociation also in the ventricle. Indeed, during the influence of the vagus nerve on such an intoxicated heart, I obtained a curve (Fig. 4) which is apt to illustrate this dissociation. We have here to deal with the transition of an alternating pulse to a normal one after a direct vagus stimulation and shortly after the inundation of the entire heart by a physiological saline solution. (In the ventricular curve this is visible.)

In my mind there is no doubt that the small elevation after the reduced ventricular contraction cannot be interpreted, either as an auricular contraction (because nowhere in this or other curves an A_s of this considerable height was observed), or as an ordinary extra-systole of the ventricle. In the latter case it cannot be explained why an extra-systole arose, nor why the preceding ventricular contraction, coming at the right time, was so exceedingly diminished in size[1]. We have here to do, undoubtedly, with a dissociation in time of two parts of

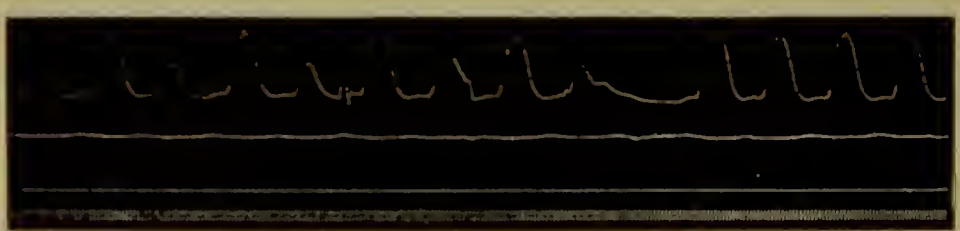

Fig. 4. Alternating pulsations of a frog's ventricle after injection of digitalis dyalisata and following a short stimulation of the vagus nerve. In the tracing a short undulation indicates an inundation of the entire heart by saline solution. Shortly after this a dissociated ventricular contraction occurs (showing 3 or 4 different tops); after this abnormal V_s the normal pulsation of the ventricle sets in.

the ventricular musculature (eventually also of Tawara's "Reizleitungssystem") and only when *after the pulsus alternans* a not complete synchronic contraction of these parts has taken place and the entire musculature comes again at the same time in the refractory period, normal contractions can follow. According to this interpretation the difference between the large and the small contractions of the preceding P.A. is to be ascribed to the fact that only in the large contractions a particular part of the muscular mass is reached by the contraction-

[1] As to the influence of extra-systole on P.A. it will be shown later, that as well in the frog as in man, extra-systole under certain conditions may cause the appearance, in other conditions the disappearance of pre-existent P.A.

wave; whereas this part of the muscle is excluded from the contraction in the small V_s.

As to a fourth form of P.A. with retarded great contraction, I do not possess, as yet, any experimental evidence.

Conclusions and remarks.

It seems to me, that in the curves given above and their analysis we have important arguments which tend to prove that on the physiological side more special research is needed regarding the conduction within the individual divisions of the heart.

For the second type of P.A. I have, I think, brought direct proof that the contraction-wave, preceding the weak ventricular contraction, is retarded, so that it becomes probable for this type of P.A. that it is the result of slowing of conductivity between the sinus and the ventricle and in the ventricle itself.

For the first type of P.A. it appears equally probable that physiologically the cause has to be sought in changed conductivity in the ventricle (not in the longer rest of the heart), by which in the weak contractions the contraction-wave is limited to a part of V.

For the third form of P.A. it appears probable that it is the result of the antiperistaltic contraction-wave, so that we have here not a quantitative, but a qualitative change in the conductivity.

Trendelenburg has stated that by stimulating artificially the ventricle at a gradually quickened rate the frequency of the ventricular rhythm may become much greater before "Halbirung" of the heart-beat occurs. The explanation of this, I think, is that the slowly increasing frequency enables the conductivity to adapt itself to the greater demands; so that the moment is delayed, when necessarily only partial contractions of the ventricle arise.

The fact that on the physiological side evidence is brought forward, that the dissociation of the ventricle under certain circumstances and the occurrence of the anti-peristaltic contraction-wave in that structure does occur, has, I think, an important bearing on our understanding of different abnormal pulses, e.g. the pulsus trigeminus.

Since partial contractions occur, it is obvious that the law of Bowditch must be limited, in so far that though every ventricular muscle fibre which contracts does so with maximal force, all the muscle bundles need not contract equally in every ventricular contraction.

When we have to interpret curves like those of Tschirjew[1], of O. Pan[2], R. Finkelenburg[3], and of Hay and Moore[4] the value of these phenomena must not be neglected. For the absence of the compensatory pause finds in the above interpretation its complete explanation.

[1] Tschirjew. *Arch. f. Physiol.* 1877.
[2] O. Pan. *Deutsche Zeitschr. f. klin. Med.* LXXVIII. p. 128. 1905.
[3] R. Finkelenburg. Quoted from Wenckebach, p. 586. 1905.
[4] Hay and Moore. *Lancet*, p. 1274. 1906.